REMARKS

The examiner considers the application to contain eight inventions or groups of inventions (Groups I-VIII) which are not so linked as to form a single general inventive concept under PCT Rule 13.1 and requires election of a single invention to which the claims must be restricted. The examiner takes the position that Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they allegedly lack the same or corresponding special technical feature, which makes a contribution over the prior art, citing Shimazaki et al., *J. Neuro. Sci.* 21:7642-7653 (Oct. 1, 2001), MacDonald et al., *J. Neurosci. Res.* 68:255-264 (2002), Zhang et al., *Stem Cells* 22:244-354 (2004) and WO 03/059376 (published July 24, 2003). This requirement for restriction is respectfully traversed. However, in order to comply, applicant elects Group I, claims 1-9, drawn to a method of generating oligodendrocytes, with traverse.

As Group I is now elected, applicants further elect the species of (i) IL-6/IL6R-IL6 chimera and (ii) 04+ oligodendrocytes, as required by the examiner. It is understood however that, upon allowance of a generic claim, applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Traversal of the restriction requirement from among Groups I-VIII is based on fact that the Groups are indeed linked by a special technical feature that makes a contribution over the prior art. Regarding the prior art cited by the examiner, the Zhang et al. (2004) and WO 03/059376 (published July 24, 2003) are not available as prior art because they are antedated by the Israeli priority document IL156430 filed June 12, 2003, provided by the International Bureau and for which priority is claimed.

The examiner has also cited the Shimazaki et al. (2001) reference for disclosing a method of culturing brain-derived neural cells in the presence of CNTF to produce glial progenitor cells including oligodendrocytes and the MacDonald et al. (2002) reference for disclosing a method of culturing oligodendrocytes from neural precursor cells of mouse embryos that are embryonic spinal cord cells in the presence of CNTF.

The claims are now amended to recite that the embryoid bodies (EB) are derived from ES cells and that the neurosphere (NS) cells are derived from ES or EB cells. Accordingly, the claims no longer read on the use of brain-derived neural stem cells or embryonic spinal cord cells.

The neural stem cells derived from brain (or spinal cord), even from embryos, are primary CNS fetal cells which are already committed to a neural fate *in vivo*. Therefore, these cells are not directly comparable to the neural cells that can be

derived from the pluripotent ES cells in cultures *in vitro*. The committed brain neural stem cells already express genes which are characteristic of glial cells, such as for example GFAP and the PDGF receptor. The composition of brain-derived neurospheres has been well described in Dromard et al, *STEM CELLS* 25:340-353 (2007). These authors show the expression of many genes which are characteristic of "radial glia", glial cells persisting in the CNS. The proteoglycan NG2 is a marker for such radial glia cells. Doetsch et al, *Cell* 97:703-716 (1999), have shown that astrocytes can be neural stem cells. This cannot be said of the ES-derived neural stem cells which do not yet express any glial/astrocyte gene marker.

Therefore, the derivation of oligodendrocytes from fetal brain (or spinal cord) neural stem cells is quite different from the derivation of oligodendrocytes from ES cell cultures, which is a *de novo* process and not the continuation of a process already initiated *in vivo*. It is a fact that, although the preparation of oligodendrocytes from CNS-isolated cells had been described many years ago, it took many years of research to succeed in obtaining oligodendrocytes from ES cells.

If, when and how to use cytokines of the IL-6 family such as CNTF also cannot be obvious based on the cited prior art. It should be noted that many cytokines have been tried in attempts to develop mature oligodendrocytes, and therefore the

use of the IL-6 type cytokines is not obvious. Furthermore, it should be emphasized that the IL6RIL6 chimera is more potent than CNTF to stimulate the development of oligodendrocyte branches. The IL6RIL6 chimera has a higher affinity for the gp130 receptor than other members of the IL-6 family and the IL6RIL6 chimera works on cells having only gp130, unlike CNTF (or LIF, Oncostatin M) which require a heterodimer of the LIF-receptor with gp130. Thus, the use of the IL6RIL6 chimera also cannot be anticipated or made obvious on the basis of studies with CNTF. Accordingly, the present claims all share a special technical feature that makes a contribution over the prior art.

Reconsideration and withdrawal of the restriction requirement are therefore respectfully requested.

Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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